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Review

Manufacture of Optically Active Materials: an Agrochemicals Perspective*

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Abstract: Against a background of the growing importance of single enantiomer agrochemicals, practical technologies for their production are reviewed. Methods range from extraction of natural products through to asymmetric synthesis and encompass physical, chemical and biological techniques.

Key words: agrochemical, manufacture, enantiomer.

1 INTRODUCTION

Single optical isomers are of special significance in bioscience applications since the desired activity generally resides in only one of a pair of enantiomers. Knowledge of this phenomenon, coupled with the technology to make and analyse for enantiomers, has led to legislative, ethical, environmental and commercial pressures to produce and use only the active isomers. This is of particular relevance to pharmaceuticals and agrochemicals,[1,2] it has been predicted that 75% of man-made pharmaceuticals will be single enantiomers by the year 2000,[3] while the corresponding figure for agrochemical launches has been estimated at a more modest 20%.[4]

Benefits from the use of single enantiomers include avoidance of gratuitous environmental contamination, separation of interfering activity or toxicity and less material to be processed with reduced costs and effluent.

This paper reviews practical methods for the production of single enantiomer agrochemicals, including under-used and emerging techniques. Some interesting pieces of technology and chemistry have barely progressed beyond the research level but need to be considered as pointers to what will become available.

1.1 Terms of reference

At this stage, it is important to define some of the bounds of this review.

Scale: This is defined by the types and levels of activities of the target materials. Manufacturing scale in this context covers the range from tens of kilograms to thousands of tonnes. At one end of the spectrum are relatively low-cost high-tonnage compounds (e.g. phenoxypropionate herbicides; thousands of tonnes per year), in the middle are chemically more sophisticated products (e.g. pyrethroid insecticides at hundreds of tonnes per year) and at the other extreme are highly potent materials such as pheromones needed in amounts of only tens to hundreds of kilograms per year. Techniques applicable at the low end of the scale are also relevant for facilitating production of initial quantities for field trials.

Agrochemical: Active ingredients of products used in the control of crop pests and diseases including herbicides, fungicides, insecticides, nematicides, molluscicides, acaricides, pest repellents, rodenticides and pheromones.

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Plant growth regulators and plant and pest hormones are also included.

The commercially dominant groups: In 1991, in terms of world sales values,[5] these are fungicides (US$ $5{\cdot}5 \times 10^9$), herbicides ($\$11{\cdot}8 \times 10^9$) and insecticides ($\$7{\cdot}7 \times 10^9$); other categories accounted for a further $\$1{\cdot}6 \times 10^9$. These figures are for all products i.e. achiral, unresolved chiral and resolved chiral. The proportion of sales accounted for by resolved chiral products is still relatively modest,[6] an example being *c.* $0·7 bn for pyrethroid insecticides in 1991.[7]

1.2 Agrochemicals and pharmaceuticals

It is useful to start the review by looking at relationships between agrochemicals and pharmaceuticals from an industrial standpoint.

The needs of the pharmaceutical industry provide a major driving force for development of new and cost-effective methods for manufacturing optically active materials. The area is moving forwards rapidly and today's pharmaceutical solution will, very probably, be tomorrow's agrochemical answer. For this reason, the state of pharmaceuticals technology is commented upon here, to supplement agrochemical examples, or where suitable agrochemical examples do not exist.

There are areas of product overlap, the most significant probably being antifungals, but ectoparasiticides (control of both animal and public health pests), antibacterials and anticoagulants should not be overlooked!

The values of agrochemicals fall roughly in the range of tens to hundreds of pounds sterling per kilogram with products such as pheromones at the top end of the scale,[8] value governs the level of sophistication of the chemistry/technology that can be brought to bear. Agrochemicals are, again very broadly, an order of magnitude lower in value than bulk drugs. However, although historically pharmaceuticals have been able to tolerate higher manufacturing costs, this may not remain the case as we enter the era of healthcare reforms and a highly competitive generics market.

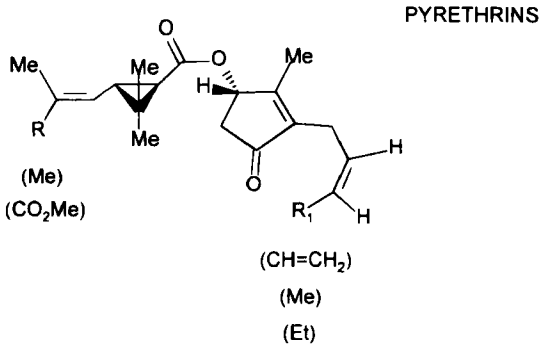


Fig. 1. The six insecticidal constituents in extracts of *Chrysanthemum cinerariafolium* (Trev.) Vis. (Dalmatian Insect Flower).

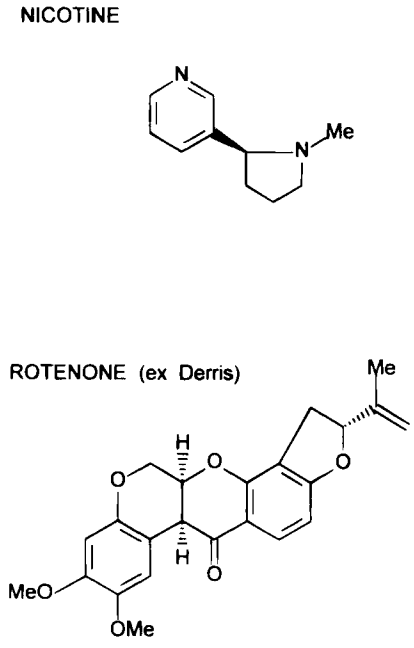


Fig. 2. Naturally occuring single enantiomer insecticides.

The situation with agrochemicals is often far from a clear-cut 'enantiomer good vs racemate bad', otherwise faster introduction of single enantiomer products might be occurring. By comparison, in pharmaceuticals, regulatory requirements make it less irksome today to develop the enantiomer; development of a racemate still requires that the individual enantiomers be rigorously tested.

1.3 A brief history of the use of optically active agrochemicals

Optically active agrochemicals have probably been in use for millennia, albeit without knowledge of the nature of the active principles.

That differential physiological responses could be obtained with enantiomers had been recognised by the end of the nineteenth century and agrochemical products containing single-enantiomer active ingredients were in use at that time, although it is doubtful whether the users recognised such differential responses.

One of the important early commodity products. pyrethrum powder, containing six homochiral active ingredients (Fig. 1), was in use in Europe from around 1820–1840 and in Persia considerably earlier; it had already attained commodity status in the nineteenth century (Table 1).[9]

Derris and nicotine (Fig. 2) are other significant 'historical' products. Derris root has long been used as a fish poison and its insecticidal properties were known to the Chinese well before rotenone was isolated in 1895.[10] It has been used since World War I to control aphids and caterpillars and before that as a sheep dip.[11]

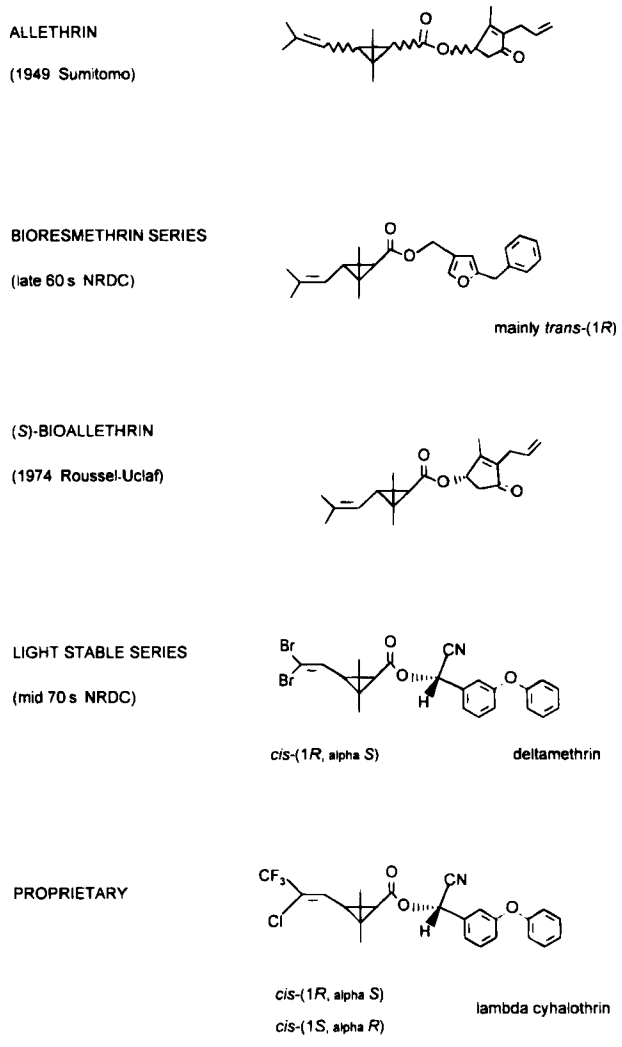


Fig. 3. Synthetic pyrethroids.

The introduction of tobacco into England in 1585 is well documented and by 1700 aqueous extracts were being used to control aphids on garden plants.[12] The difference in the toxicities of nicotine enantiomers was recognised by Mayor in 1904.[13] By 1910, nicotine sulfate was being marketed as the most popular form of the insecticide.[14] Its decline was due to the spectacular growth of the synthetic pesticide industry following World War II and, with DDT at less than 20% of the price of nicotine, sales of the latter had declined to only a few hundred tonnes per year by 1970.[15]

Development of modern agrochemicals really began only with the advent of synthetic organic pesticides in the 1930s and to carry the story of single enantiomer agrochemicals forward we have to look principally at the development of synthetic pyrethroids (Fig. 3). The rapid knock-down and high activity of the natural pyrethrum led to intense interest in the synthesis of more stable alternatives. In 1949 allethrin was introduced by Sumitomo as a mixture of isomers. Work at Rothamstead by Elliott and co-workers then led to a new group of compounds, which included bioresmethrin (mainly the active *trans*-(1R) isomer of resmethrin) and these became commercially available at the end of the 1960s. Further work led to a second, light-stable, series introduced in the mid 1970s, of which the key products were permethrin, cypermethrin and the fully resolved deltamethrin. Also at this time, allethrin was developed as the single, active isomer. Further development of a range of proprietary compounds brings this strand of the story up to date; all the resolved, or partially resolved, pyrethroids were obtained by resolution/crystallisation techniques.

Following on from the pyrethroids, other single enantiomer products were introduced, most notably the aryloxypropionate herbicides.

It had become apparent that there could be significant benefits in activity/cost efficacy resulting from a switch to single enantiomers and that, by the 1970s, it was well within the industry's technical capabilities to achieve this. By the early 1990s the stimulus to make this switch was being reinforced by environmental and regulatory pressures.

2 METHODS

Today, single enantiomers may be generated in five main ways, i.e. from the 'pool' of existing materials; by classical resolution and associated techniques; by a range of biological methods; by chemically catalysed asymmetric synthesis and by physical separation methods.

Until quite recently, ignoring production by fermentation or extraction from natural products, and with the exception of some rare examples of conglomerates

TABLE 1
Some Details Concerning Use of Pyrethrum

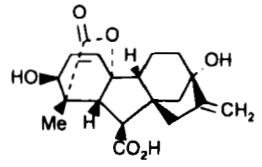
	Year	*Tons*
US imports of 'insect powder'	1885	300
US imports of 'insect powder'	1919	1500
Japanese production	1935	14000
World-wide production	1972	22000
(Dried flowers contain 10–20 g AI kg^{-1} plant material)		

GIBBERELLINS

(ex *Gibberella fujikuroi*)

gibberellic acid

(PGR)

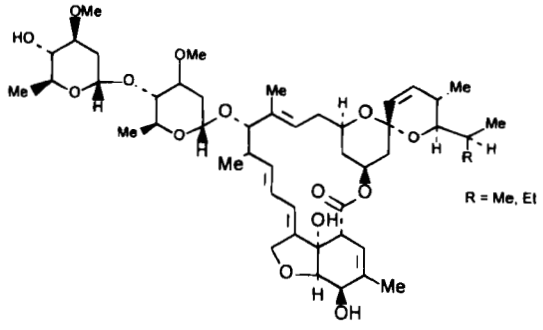


AVERMECTINS

(ex *Streptomyces avermitilis*)

abamectin

(insecticide, acaricide)



blasticidin-S

kasugamycin

natamycin

polyoxins

validamycin

mainly antifungals

(ex *Streptomyces spp.*)

Fig. 4. Examples of agrochemicals obtained by fermentation processes.

resolved by direct crystallisation, optically pure chemicals required the stoichiometric use of enantiomerically pure substances either as building blocks or reagents, and especially as resolving agents. Today, biological and chemical catalysis increasingly hold the key to economic manufacturing processes.

This topic may be explored either by studying case histories or by determining the advantages and limitations of presently available technologies and how well they meet current needs. The latter approach has been chosen in order to try to keep the merits of different methods in perspective. There are several ways to subdivide such an analysis, none of which is entirely tidy, but the following will serve to evaluate the present position.

2.1 Natural products by extraction

Three of the principal plant extracts, pyrethrins, rotenone and nicotine, all of which are insecticides, are shown in Figs 1 and 2. The technology by which these are extracted is generally trivial, as exemplified by isolation of nicotine from tobacco with solvents or by steam distillation.

2.2 Natural products ex fermentation

Figure 4 shows some secondary metabolites which are of agrochemical interest obtained by fermentation processes. In addition to gibberellins (ex *Gibberella fujikuroi* (Saw.) Wollenw.) and avermectins (ex *Strep-*

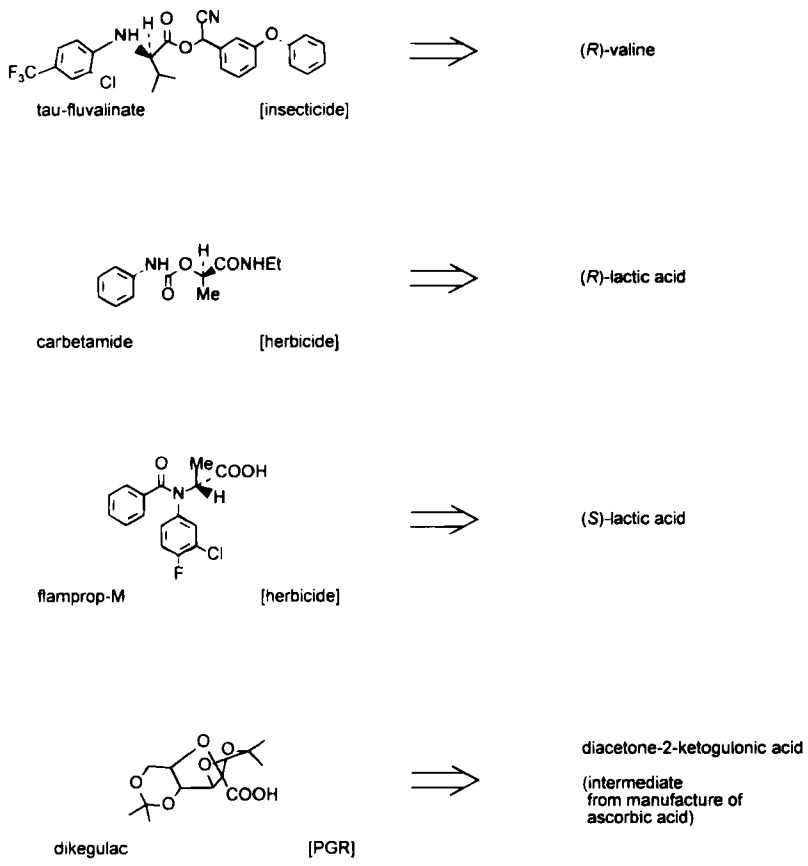


Fig. 5. Examples of agrochemicals obtained using building blocks from the chiral pool.

tomyces avermitilis M. S. & D.), a whole range of useful compounds (mainly antifungals) may be obtained using *Streptomyces spp.* Structures in this class are highly chiral and defy economic chemical synthesis. By contrast, however, fermentation can be an economic technique and was the method used for the first industrial production of an optically active compound, L-lactic acid, in 1880,[16] a primary metabolite and a compound of interest today as a chiral building block because it is produced so cheaply from D-glucose. D-Lactic acid is also produced by fermentation for conversion to (*S*)-2-chloropropionic acid required for a range of aryloxy-propionate herbicides (see below).

Although secondary metabolites are an order of magnitude more costly to produce than primary metabolites such as lactic acid, on the 1000-tonne scale costs of $<$£50 kg^{-1} are still achievable.[17] If, in addition, use of fermentation technology is coupled with strain enhancement by genetic engineering, to increase the titre of the desired substance, it might reasonably be expected that the technique will continue to be used and indeed extended; it is by no means incompatible with the cost targets for some agrochemicals.

2.3 Chiral pool

The 'chiral pool' customarily refers to relatively inexpensive, readily available optically active natural products (carbohydrates, terpenes, alkaloids, hydroxy acids and amino acids); desirably these should be available with a high enantiomeric excess (ee) and in both enantiomeric forms. Representative materials are shown in Table 2. In reality, of course, the pool includes all commercially available and in-house optically active materials which have a diversity equalling their natural

TABLE 2
Representative Commercially Available Chiral Pool Materials

Material	*Approx. price*[a] (*US$ kg*$^{-1}$)
Ascorbic acid	17
(+)-Calcium pantothenate	24
(−)-Carvone	22
Dextrose	1·2
Ephedrine hydrochloride	64
(+)-Limonene	4·5
L-Lysine hydrochloride	2·7
Mannitol	7·4
Monosodium glutamate	2·5
Quinidine sulphate	136
Quinine sulphate	82
Sodium erythorbate	9
Sorbitol	1·6
L-Threonine	8–45 (depends on grade)
L-Tryptophan	50

[a] From Ref. 56.

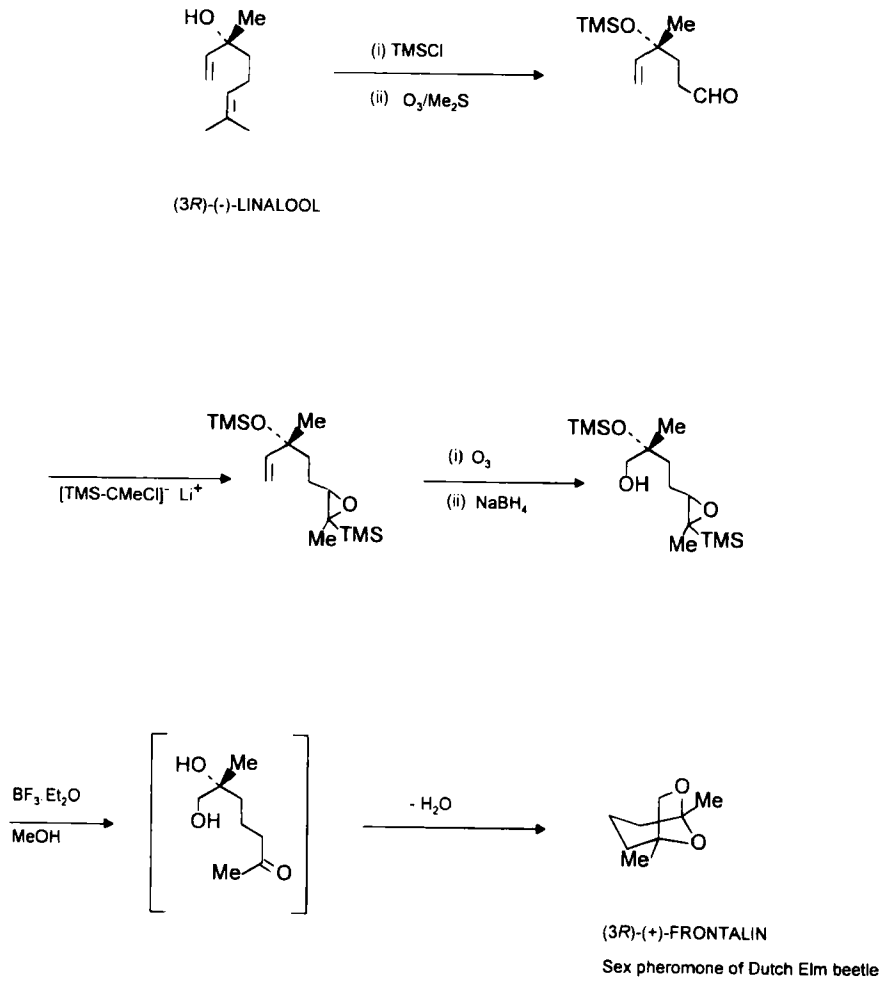


Fig. 6. Synthesis of (3*R*)-(+)-frontalin.

counterparts. For example, in the development by Roussel-Uclaf of a process for deltamethrin, *trans*-chrysanthemic acid was resolved classically using an in-house 'pool' material which was the unwanted isomer of chloramphenicol base. Many conventional pool materials, such as ephedrine and (−)-menthol, have also had their availability considerably augmented by manufacture. The 'pool' overlaps most other categories and is, in turn, fed by them; it clearly supplies the two groups of agrochemicals discussed above.

Pool materials are put to many uses, being widely employed as resolving agents and functioning as 'synthons', where they are incorporated, more or less intact, into the product structure. They also serve as auxiliaries (see below) where their chirality is transferred into the target molecule and, ideally, is then recovered and re-used; additionally they provide the key elements of many chiral catalysts.

Across all sectors, amino acids are probably the most widely used pool synthons (cf. tau-fluvalinate, Fig. 5). Carbohydrates and terpenes are too elaborate for most purposes and are usually only available as one enantiomer; they are rarely used as building blocks. Alkaloids are largely used as resolving agents or as components of chiral catalysts.

All the proteinogenic L-amino acids are available commercially on scales ranging from 10 to 10^5 tonnes $year^{-1}$ and D-amino acids are becoming increasingly available; many of the technologies for amino acid production will, in principle, produce either enantiomer.[18]

Tartaric acid, despite its abundance and its long history within organic stereochemistry, has found little use as a building block. It has featured most often as a resolving agent, and latterly as a source of chirality in catalysts for asymmetric synthesis.

Use as building blocks to obtain optically active products is usually straightforward and without major synthetic challenges, within the constraint of selecting a route which avoids downstream racemisation; however, it is largely a matter of luck whether a given target can utilise a pool material in this way. Figure 5 shows examples of 'pool' use for building blocks incorporated with minimal modification of the original structure.

Many further *potential* applications to materials of agrochemical relevance could be provided, an example being the synthesis of (3*R*)-(+)-frontalin, the sex pheromone of the Scolytid beetles which transmit Dutch elm disease, from the terpene (3*R*)-(−)-linalool (Fig. 6).[19]

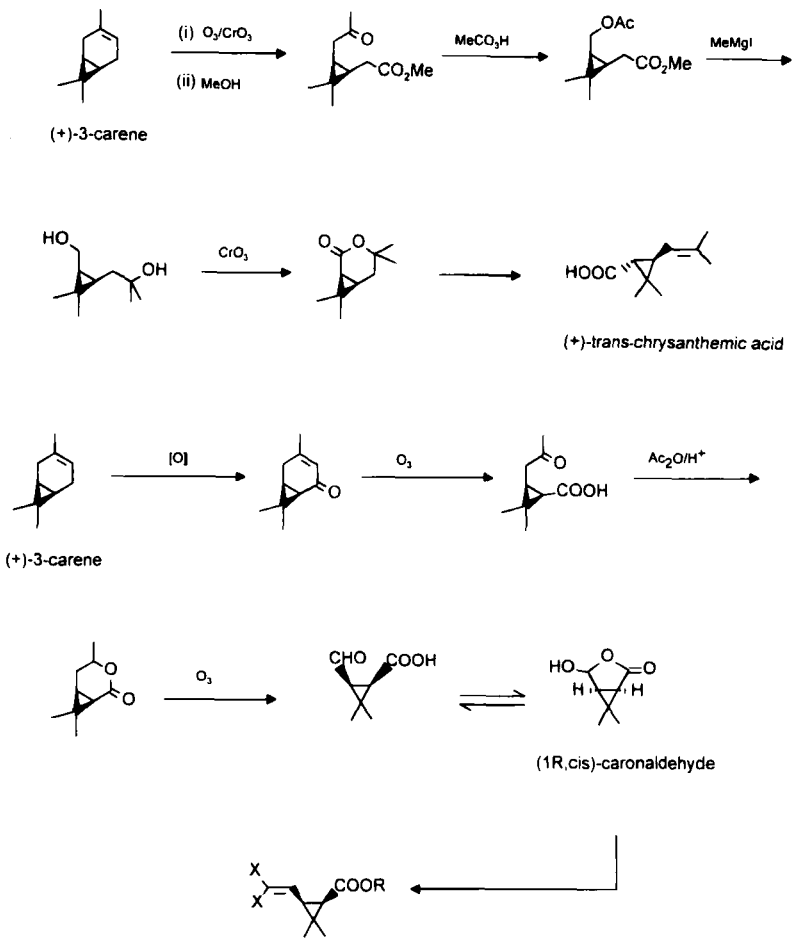


Fig. 7. (+)-3-Carene as a building block for pyrethroids.

Terpenes are of special interest in that the structural feature of many of them which has invited attention is the occurrence of geminal dimethyl groups in a chiral environment, and considerable effort has been expended in trying to exploit them in pyrethroid syntheses (Fig. 7).[20,21] Perhaps not surprisingly, a lot of this work has emanated from Indian laboratories since (+)-3-carene of high ee, a particularly useful building block in this

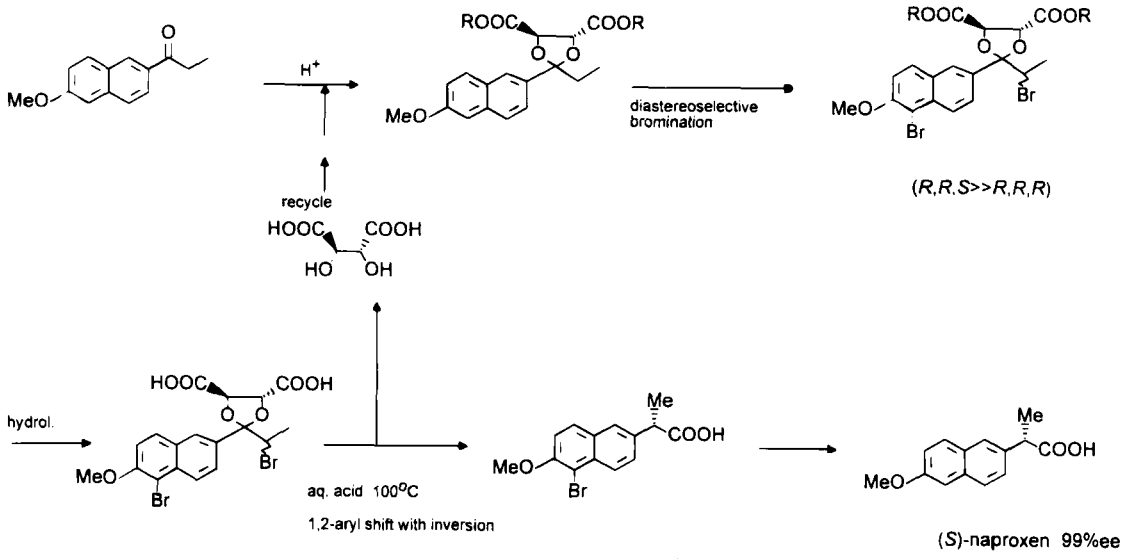


Fig. 8. Tartaric acid as a chiral auxiliary (Zambon naproxen process).

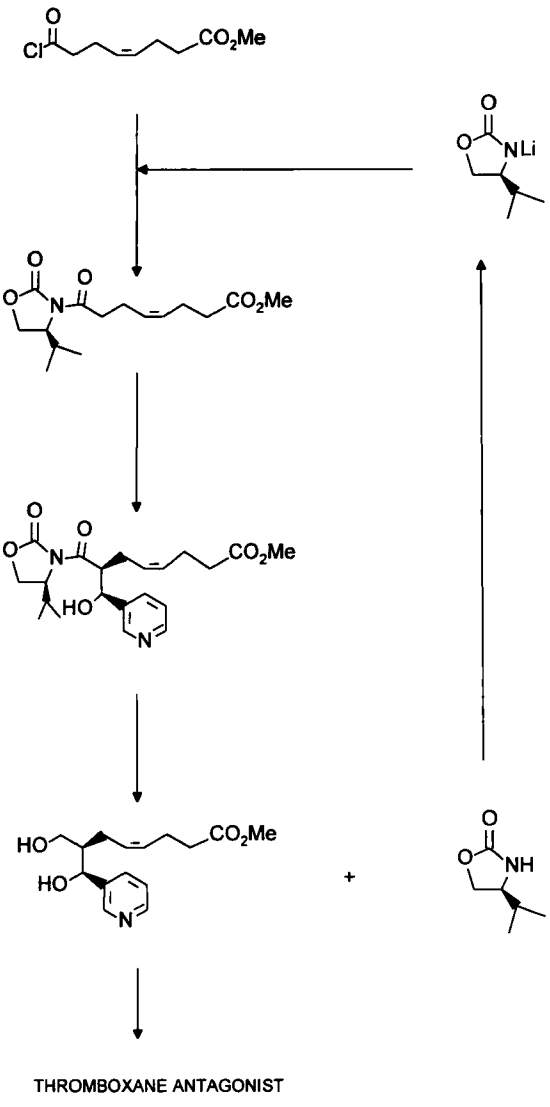


Fig. 9. Use of Evans' auxiliary.

context, constitutes about 60% of Indian turpentine, the production of which is in the region of 6000–9000 tonnes year^{-1}.[21]

2.4 Chiral auxiliaries

Auxiliaries are used stoichiometrically; chirality is transferred without loss into a new stereogenic centre and the auxiliary is then, ideally, recovered for re-use. Figure 8 shows an example where a cheap 'pool' auxiliary is used and is easily recovered[22] whilst Fig. 9 shows a use of the more sophisticated Evans' auxiliary which has been applied on the pilot scale.[23] Both examples come from the pharmaceuticals area.

Application of any chiral auxiliary on a large scale depends on there being an efficient non-destructive recycling process; for example, the Evans chiral oxazolidinones may be recycled with $\geqslant 90\%$ recovery in favourable cases. The auxiliary should also be of minimal molecular weight and, ideally, be available in both enantiomeric forms, considerations which apply equally to resolving agents.

Many other synthetically versatile auxiliaries are available and are widely used for small-scale syntheses; eg SAMP ((*S*)-1-amino-2-methoxymethylpyrrolidine) and RAMP (the *R* enantiomer) hydrazones,[24] but they are generally still too expensive for large-scale use. Auxiliaries becoming available at the 100-kg scale include bornane-10, 2-sultam and oxazolidinones.[25]

In principle, auxiliaries give double the yield of that from a resolution-based approach but, in considering the overall efficiency and economics of using an auxiliary, the different chemistries employed in reaching the target must also be taken into account. Even if auxiliary and resolving agent are of equal cost the auxiliary

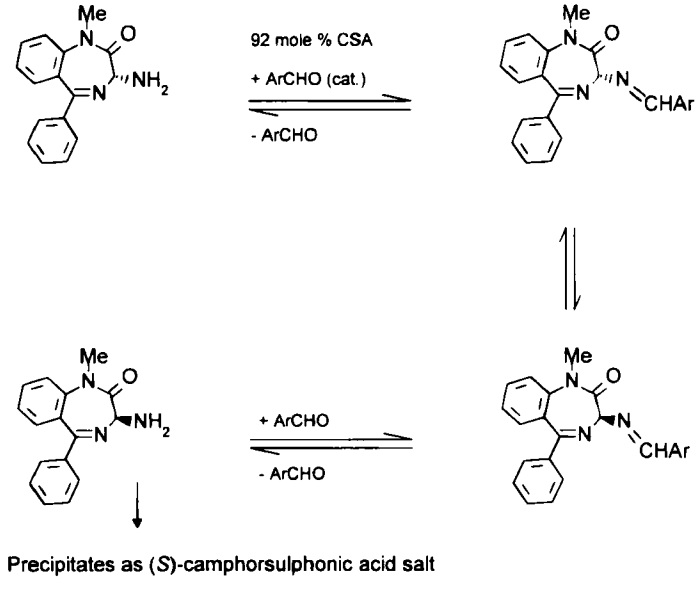


Fig. 10. Classical resolution with in-situ racemisation.

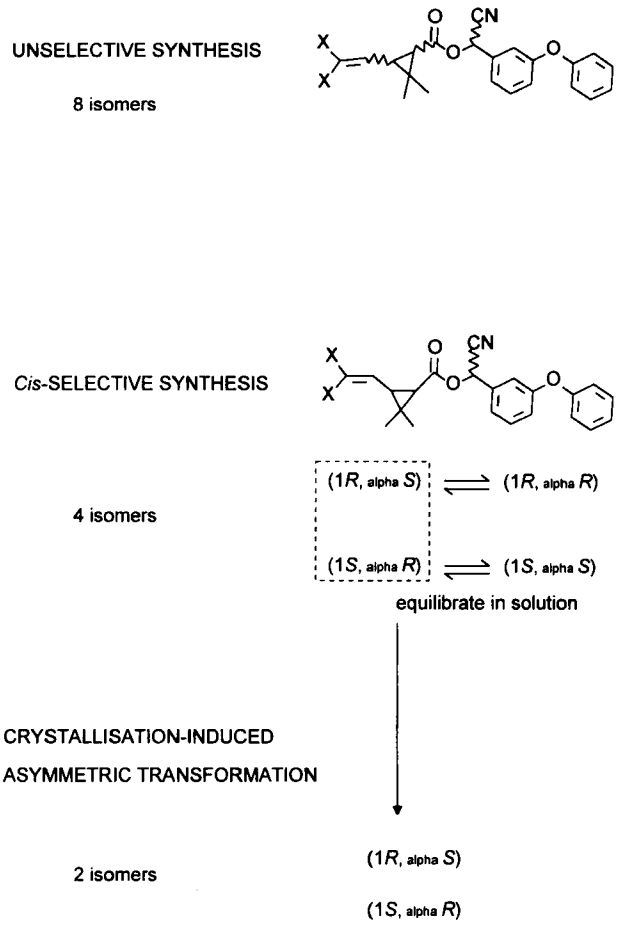


Fig. 11. Crystallisation-induced asymmetric transformation.

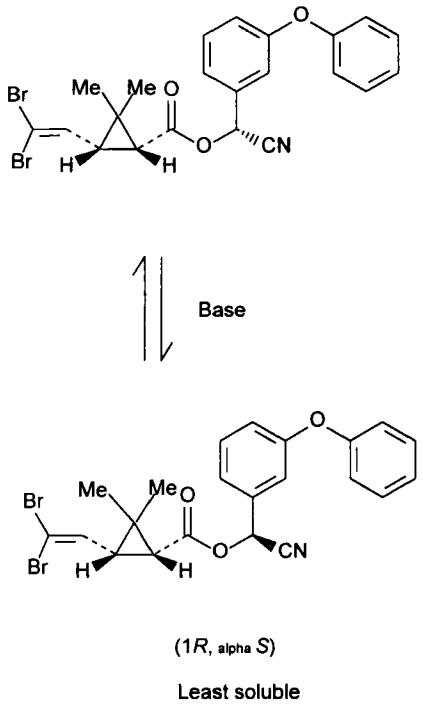


Fig. 12. Crystallisation-induced asymmetric transformation of deltamethrin.

approach could still be inferior. However, there is no reason why auxiliaries should not feature in larger-scale manufactures, as the examples in Figs 8 and 9 demonstrate.

2.5 Non-biological resolutions

2.5.1 Classical resolution

The potential of classical resolution for economic manufacture is probably underestimated. Even today, a greater *number* of chiral products are produced by classical resolution than by any other method. A recent literature survey showed that the number of patents being granted for resolution processes exceeds that for asymmetric synthesis[26] and is consistent with the results of another survey of single enantiomer drugs in development at a major pharmaceutical company which showed that 57% were being obtained by ionic or covalent resolution.[27]

The main requirements for a resolving agent are that it should be cheap (per mole), readily available and have a high ee. It should preferably be available in both enantiomeric forms, but this restriction can sometimes be circumvented by changing the solvent to allow either enantiomer to be selected by one isomer of the resolving agent.

The theoretical 50% yield limit can be breached if the unwanted enantiomer can be racemised, ideally by combining resolution with racemisation to give an asymmetric transformation. A well-known example in the pharmaceuticals area which demonstrates the elegance of the approach comes from the Merck synthesis of a candidate cholecystokinin antagonist (Fig. 10).[28] Here, a catalytic amount of an aldehyde facilitates racemisation in solution *via* the imine, and the desired (*S*)-amine continuously crystallises as its (+)-camphorsulfonic acid salt. Devices such as this can transform resolution economics. The same considerations obviously apply to biological resolutions as discussed below.

In all types of resolution the stage which allows most efficient recycle will dictate where recycling is carried out; otherwise it should be done as early as possible to minimise the total amount of material being processed.

Crystallisation-induced asymmetric transformations are important in the production of several pyrethroids, where they can be used to enhance the activity of isomer mixtures (Fig. 11).[29] The activity compared with that of an unselectively synthesised isomer mixture may, in the first instance, be enhanced by a *cis*-selective synthesis and then further enhanced, using this technique, to produce a two-isomer mixture, thereby approximately doubling the proportion of the (most active) *cis*-(1*R*, α*S*) isomer in the mixture. Where the cyclopropane moiety is resolved, the single most active isomer can be isolated, as in the final step of the Roussel-Uclaf process for deltamethrin (Fig. 12).[30]

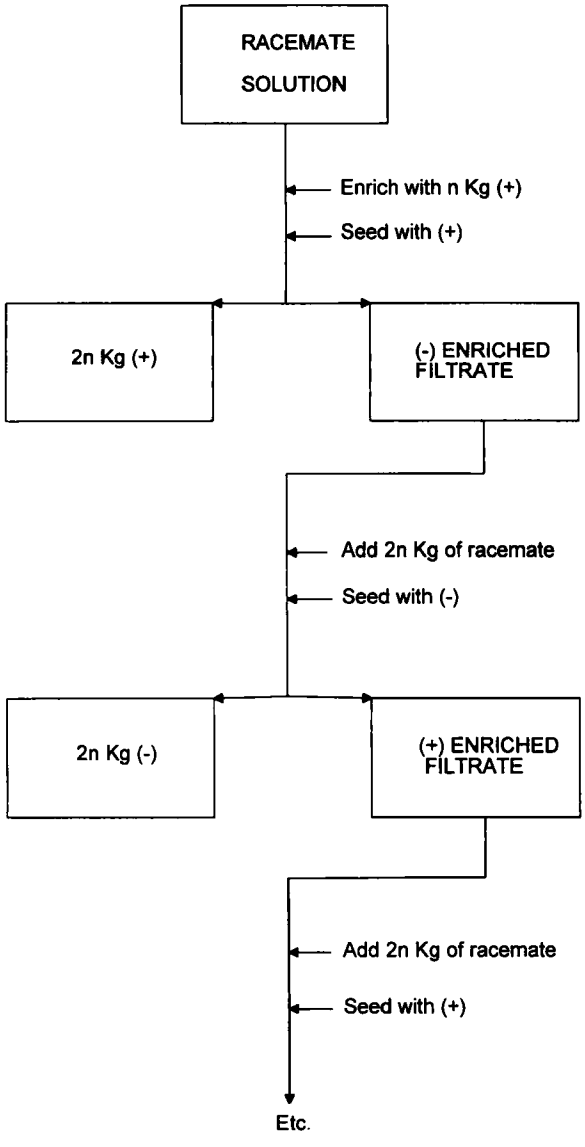


Fig. 13. Resolution by direct crystallisation.

It is fortunate that the active pyrethroid diastereomers are the less soluble. Had the converse situation applied and the unwanted isomer or isomer pair been the less soluble, it would have been necessary to first enrich the mixture by filtering off the unwanted material and recycling this in a separate step, an altogether less attractive processing operation.

2.5.2 Resolution by direct crystallisation

If feasible, resolution by direct crystallisation is extremely appealing, at least on paper, though it is likely to be technically demanding to operate. Auxiliaries and reagents are not required and the method does not depend for success on the presence of functional 'handles'. However, it only works for substances existing as crystalline conglomerates, that is where individual crystals contain only the (+) or (−) isomer.[31] There are several operational variations of the method and Fig. 13 illustrates one of these. In the phar-

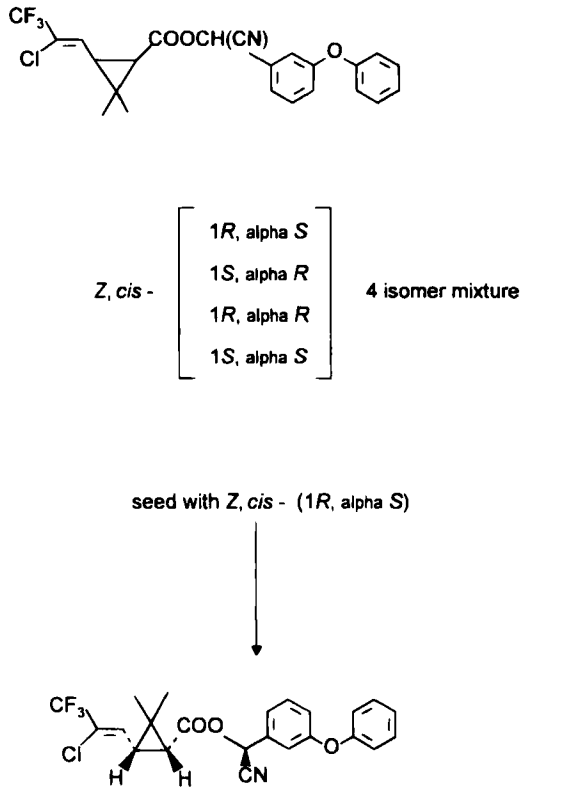


Fig. 14. Direct crystallisation of *cis*-(1*R*, alpha *S*)-isomer of cyhalothrin.

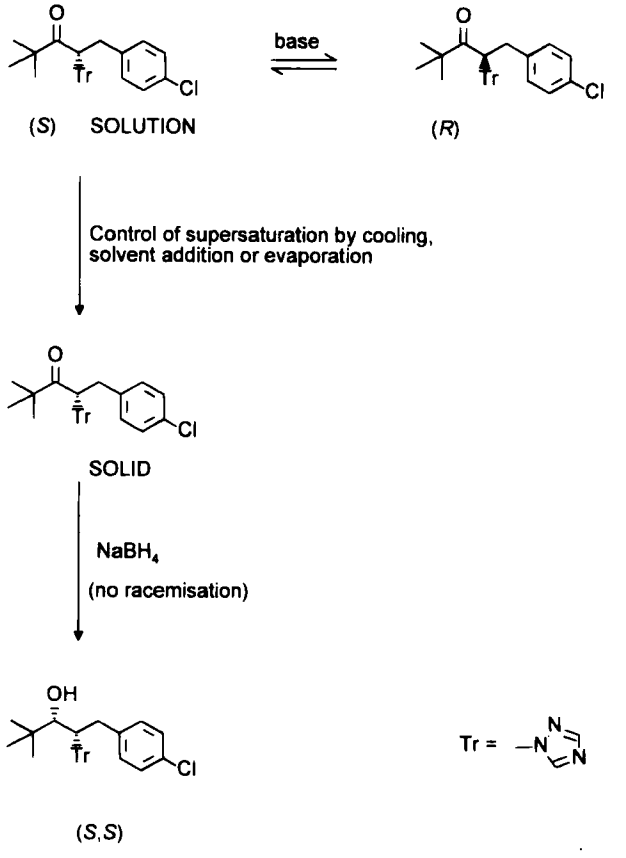


Fig. 15. Crystallisation-induced asymmetric transformation (resolution of paclobutrazol intermediate).

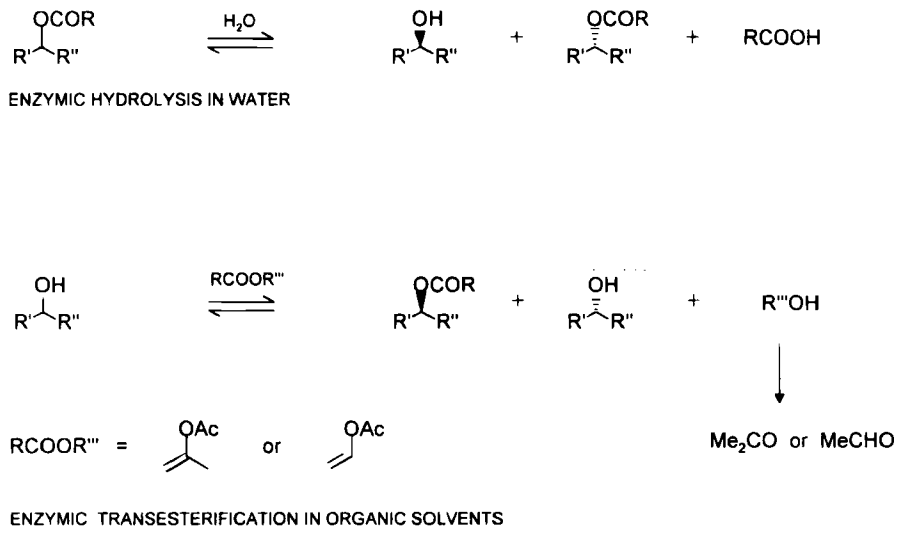


Fig. 16. Stereochemical complementarity of biological resolutions.

maceuticals area, direct crystallisation has been used to resolve chloramphenicol base[32] and an intermediate for L-α-methyldopa[33] whilst elsewhere it has been used for L-glutamic acid on a scale in excess of 10000 tonnes year^{-1}.[34]

A practical limitation of direct crystallisation is the build-up of impurities and the tolerance to these of the crystallisation process; very fine temperature control may also be needed. The method is of limited applicability, in that the occurrence of conglomerates cannot be predicted and has been estimated at only about 10% of all crystalline racemates. However, the frequency of its occurrence amongst salts may be two or three times that for covalent compounds, which provides a basis for increasing the chance of discovering the necessary conglomerate.[35]

An example from the author's own work (Crosby, J., unpublished) was direct crystallisation of the active *cis*-(1*R*, α*S*) isomer of cyhalothrin from the initial four-isomer mixture (Fig. 14). However, because of the difficulty of recycling the unwanted *cis*-(1*S*, α*R*) isomer, this does not offer any economic advantage over crystallisation of the (1*R*, α*S*)/(1*S*, α*R*) isomer pair.

Another example of a crystallisation-induced asymmetric transformation is that of a triazolyl ketone intermediate in the preparation of paclobutrazol, the essence of the method being shown in Fig. 15.[36] Note that the successful realisation of this process required (i) that the ketone crystallised as a conglomerate, (ii) rapid base-catalysed racemisation and (iii) sterospecific reduction of the ketone without racemisation.

2.6 Biological methods (resolution and asymmetric synthesis)

The advantages and disadvantages of biological methods have been described elsewhere,[18,37,38] the major attraction in the present context being enantioselectivity.

Biological methods are certainly not new as economic technologies[39] and there is no inherent reason why they should not be used; overall, a greater *tonnage* of optically active materials is probably produced in this way than by any other method but, even so, it has not been fully exploited, even in the simpler applications.

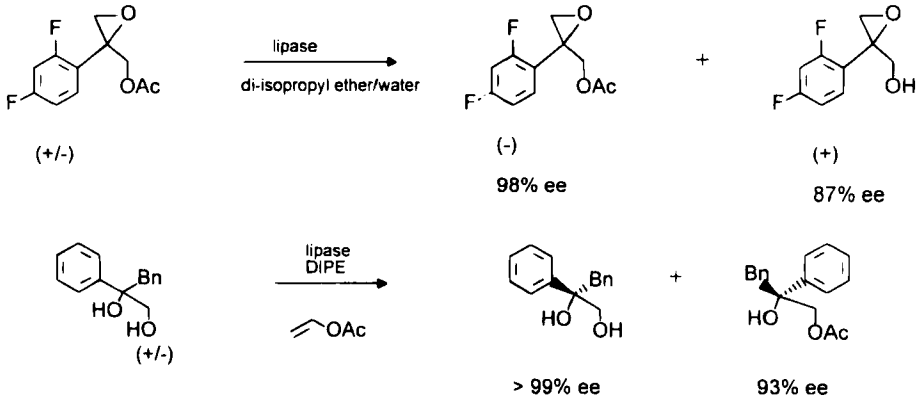


Fig. 17. Enzyme-catalysed resolutions.

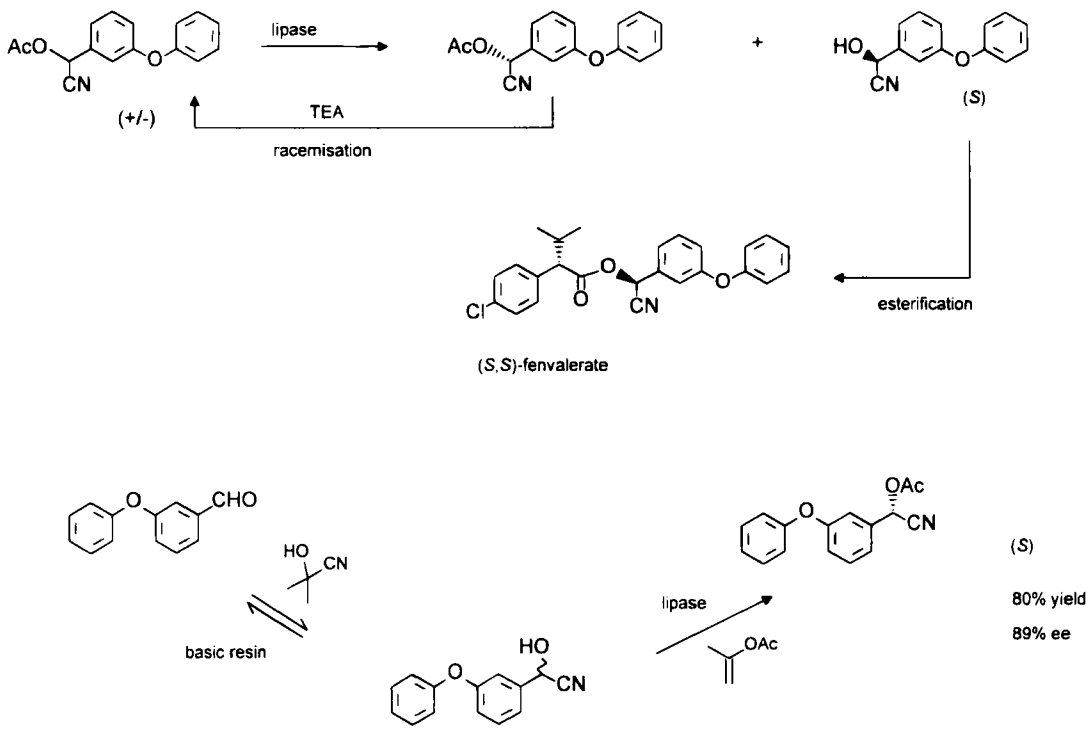


Fig. 18. Biological resolution combined with racemisation of the unwanted isomer.

Until the 1970s, it was widely assumed that enzymic synthesis could be performed only in aqueous media. This situation was changed in the mid-1980s by the work of Klibanov, who used organic media successfully,[40] and this increased the processing options. Developments in recombinant-DNA technology, which allow for enhanced expression of selected enzymes, and in protein engineering to custom-design enzymes, also further increase the basis for a commercially attractive technology.

Biological methods are divided into those which do, or do not, require co-factors. For the latter, typically hydrolase-catalysed resolutions, off-the-shelf enzymes may suffice. Commercially available esterases and lipases have a wide range of substrate specificities and are usually stable; in addition, new and useful 'non-nameplate' activities continue to be discovered,[41] further extending their usefulness. If the desired selectivity is not available from a commercial enzyme, then a capability to hunt out and optimise a source of the required activity is needed and access to a biological skill base becomes a pre-requisite. This is even more important if the target requires a redox reaction in that enzymes which catalyse these have a number of features which restrict their commercial application. Thus, in addition to the need to recycle expensive cofactors the enzymes are often multi-component and unstable, limiting cell-free application.

Large-scale applications to fine chemicals manufacture have been confined mainly to hydrolytic processes, which are readily sited in conventional chemical plant. Across the industry, and up to the mid-1970s, there was only a handful of successful applications, but the past twenty years have witnessed a dramatic increase, especially if processes which have progressed to at least semi-technical scale in the past five years are included.

2.6.1 *Resolution*

Whenever faced with a classical resolution, the possibility of carrying out a biological resolution instead should always be considered because there is a good prospect of it being cheaper. For example, if ester, acid or alcohol functionality is present, it is not unrealistic to aspire to a bio-resolution which gives *c.*90% recovery of the required enantiomer in a single step and with very high ee. Few classical resolutions match such efficiency; in addition to often needing several crystallisations to achieve optical purity, with attendant yield losses, they incur the cost of recovering the resolving agent.

A particular benefit conferred by bio-resolution has been in the separation of alcohol enantiomers; 15–20 years ago, most were either converted to hydrogen phthalate derivatives and then resolved as diastereomeric salts with alkaloid bases, or converted to other covalent derivatives *via* reaction with chiral isocyanates, acid chlorides, etc. These approaches are not attractive for large-scale use because of the additional steps and reagent costs. Today, if an alcohol has to be resolved, bio-resolution, either of the free alcohol or of a derived ester, would be the first choice, possibly run as a non-aqueous process.

The stereochemical complementarity of running the process in either the synthetic or hydrolytic direction should also be recognised. If the enzymic hydrolysis

leaves the required enantiomer as the ester, then running the process in the direction of ester-formation will leave the required alcohol enantiomer unreacted and save process steps (Fig. 16).

Figures 17 and 18 show examples of possible utility in agrochemicals synthesis/manufacture. In Fig. 17 are two examples of enzyme-catalysed resolution of alcohol intermediates for azole antifungals. The first, a pharmaceutical example,[42] uses ester hydrolysis, whilst the second employs the complementary approach of lipase-catalysed stereo- (and regio-) selective esterification in an organic medium, using vinyl acetate to ensure irreversibility.[43]

Figure 18 shows further examples, with the additional refinement of racemisation of the unwanted enantiomer. In the first, the acetate of racemic *m*-phenoxybenzaldehyde cyanohydrin is hydrolysed enantiospecifically to furnish a key intermediate for fenvalerate. The unwanted (*R*)-acetate is easily racemised by organic base without producing the aldehyde.[44] The second example employs in-situ racemisation, *via* reversible cyanohydrin formation, to achieve a one-pot synthesis of the required (*S*)-acetate of *m*-phenoxybenzaldehyde cyanohydrin.[45]

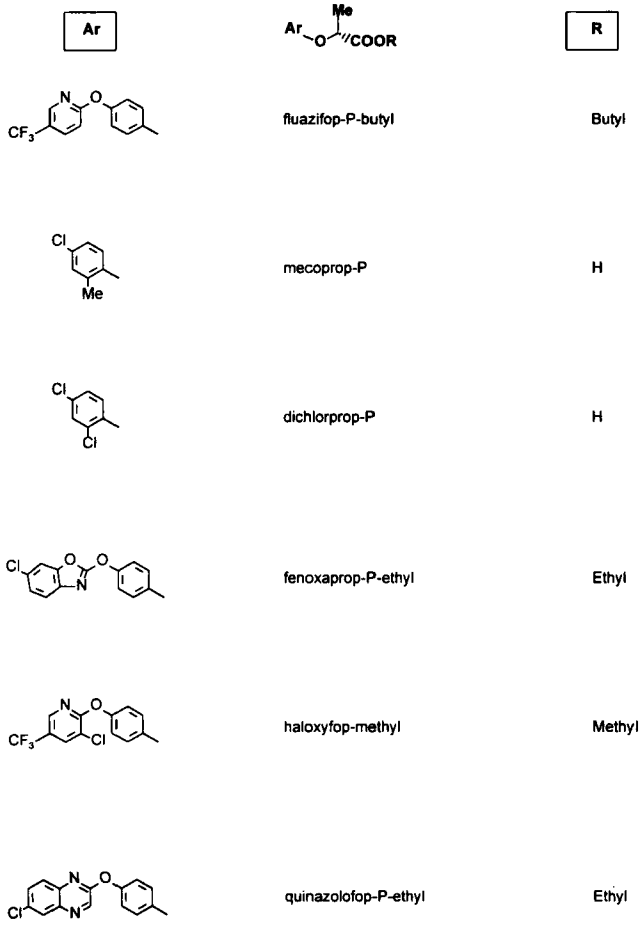


Fig. 19. Examples of single enantiomer aryloxypropionate herbicides.

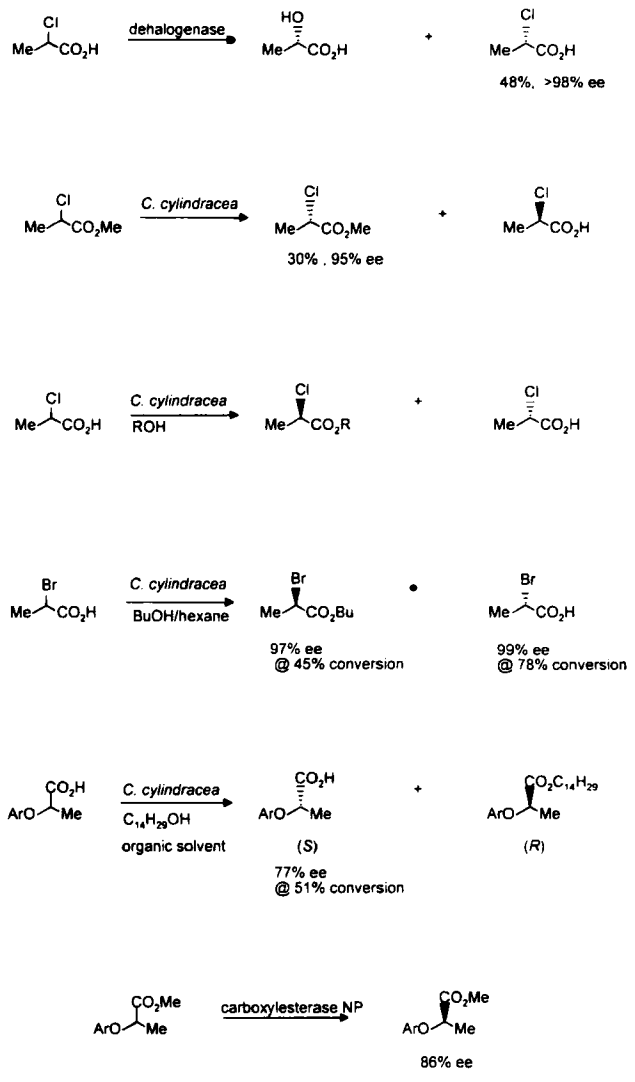


Fig. 20. Examples of biological resolution approaches to aryloxypropionates and their key building blocks.

Another group of products which has stimulated wide investigation of bio-resolution approaches is the aryloxypropionate herbicides (Fig. 19).

Figure 20 shows a range of approaches to the bio-resolution of the key building blocks, 2-chloropropionic acid and its esters, and also to the resolution of aryloxypropionates themselves. *Candida cylindracea* lipase has been employed for resolution *via* both hydrolysis[46] and ester formation,[47] the latter gives the free acid as the required (*S*)-enantiomer. Resolution of 2-bromopropionic acid[48] has also been investigated, but it is difficult to envisage either this process or resolution of the more elaborate aryloxy species,[49,50] being cost-competitive unless accompanied by efficient recycles.

2.6.2 Synthesis

Biological methods for asymmetric synthesis, rather than resolution, may be subdivided into those requiring oxidoreductases and those using a variety of other,

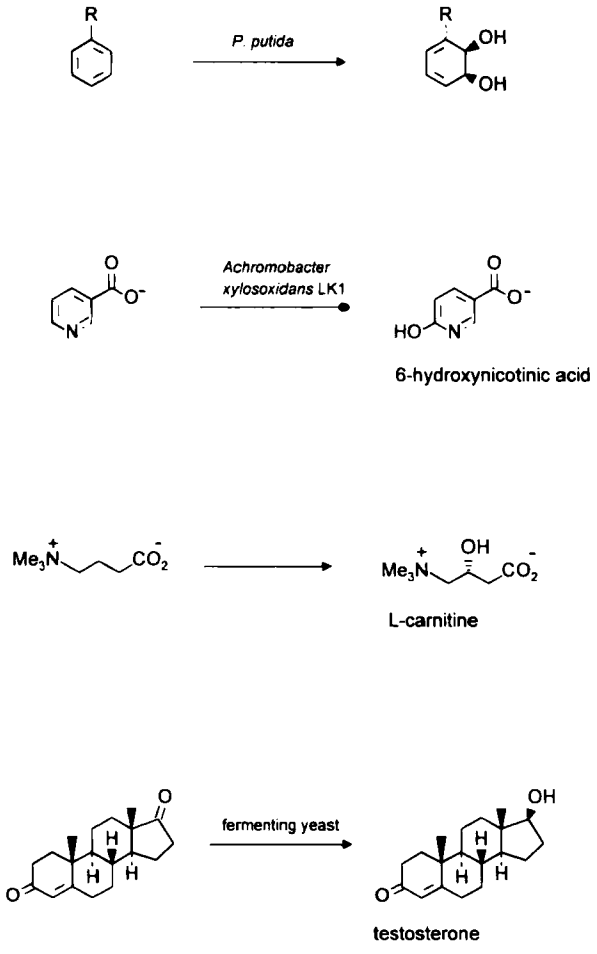


Fig. 21. Use of oxidoreductases.

easier to apply, enzymes such as hydrolases for 'desymmetrisation' of *meso* and prochiral substrates.

Oxidoreductases require stoichiometric amounts of expensive cofactors and, as a result, are generally used in whole cells (both resting and fermenting). The stereochemical capabilities of this group of enzymes are tantalising, but the technology at present is probably the least able to meet the need for economic manufacture of moderately priced products. In *general* terms, for large-scale use, whole-cell systems suffer from a number of disadvantages (Table 3). This is not to say that oxidoreductases cannot be used if the product value justifies it, as the examples in Fig. 21 testify. It has already been noted that fermentation technology, to produce secondary metabolites, is not necessarily ruled out for agrochemicals production, but when all the fermentation costs are associated with just one chemical transformation within the overall synthesis, this is far less likely to be economic.

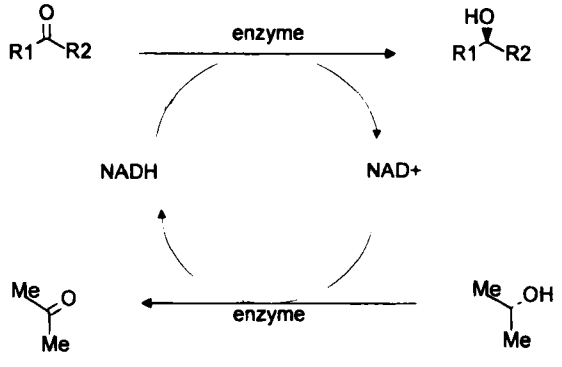


Fig. 22. Enzyme-coupled regeneration of cofactor.

TABLE 3
Disadvantages of Whole-Cell Systems

Dilute and Unproductive
High effluent loads
Lack stability/multicomponent catalysts (poorly characterised)
Not available off the shelf
Difficult process development
Need fully integrated skill base
Poor mechanical properties
Difficult separations

Stoichiometric use of cofactors such as NADH would be prohibitively expensive but, when isolated enzymes are used, enzyme-coupled methods for cofactor regeneration have been developed; cf. Fig. 22.

Currently, this area of technology is being vigorously challenged by non-biological asymmetric synthesis (below). There are, however, a number of approaches to enzyme-mediated asymmetric synthesis which it is easier to envisage being applied (Fig. 23).

Where they can be used, 'desymmetrisation' reactions such as (1)[51] and (2)[52] in Fig. 23 are clearly attractive. Reaction (1) poses no particular problems, and nitrile hydrolysis has been applied on a very large scale for the production of acrylamide from acrylonitrile. In general, however, nitrilases have been under-exploited because of lack of commercial supplies and the failure, until recently, to appreciate properly their potential for enantioselective synthesis.

Use of oxynitrilases in the synthesis of chiral cyanohydrins from aldehydes ((3), Fig. 23) has been developed to the semi-technical scale by Peboc but the author is unaware of any large-scale use. Whilst the (*R*)-oxynitrilase is readily available, the (*S*)-analogue is relatively expensive.

Another useful technology, which has been developed by Celgene for a broad range of amine products at the multi-100-kg scale, is transamination ((4), Fig. 23).[53,54] An additional advantage of this process is that it may be run in reverse to effect amine resolution.

2.7 Non-biological asymmetric synthesis

Use of homogeneous, chiral, transition-metal-based catalysts emerged about twenty years ago and advances have been spectacular, particularly in the past five years. Notable successes include the asymmetric hydro-

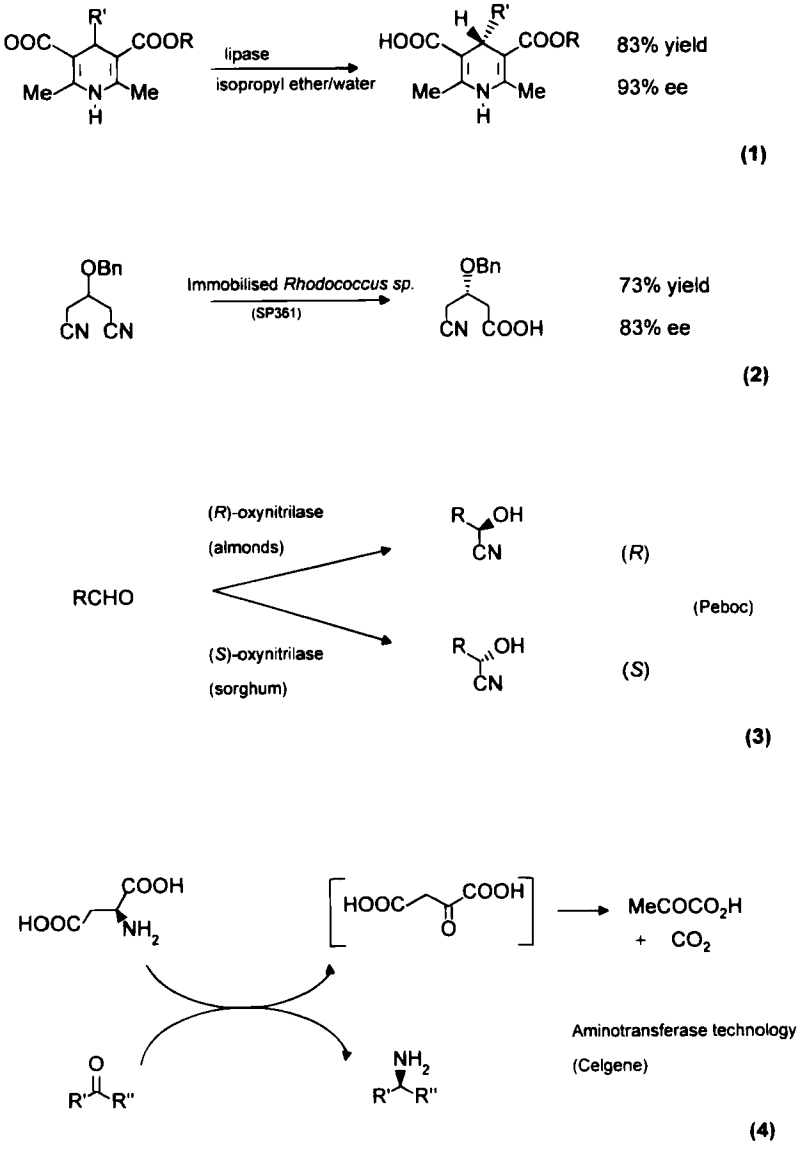


Fig. 23. Enzyme-mediated asymetric synthesis.

genation of dehydroamino acids, the Sharpless epoxidation and dihydroxylation processes, the Jacobsen epoxidation, the Sumitomo cyclopropanation and the Noyori hydrogenation reactions.[55] The efficiencies of the catalysts match those of enzymes and processes are economically competitive, with several operated on a large scale (Table 4), whilst others are being scaled up. In an agrochemicals context, the scope to achieve cheap, large-scale manufacture can be gauged by the fact that the Takasago (−)-menthol process (1000-tonne per annum) must be competing with the natural product at \$10–12 lb^{-1}.[56] Very high turnover numbers are obtained, making the contribution to product cost from the catalyst correspondingly small.

TABLE 4
Examples of Catalytic Asymmetric Synthesis Operated on a Large Scale or at an Advanced Stage of Development

Hydrogenation	Monsanto, Takasago
Epoxidation	ARCO (Sharpless), Sepracor (Jacobsen)
Cyclopropanation	Sumitomo
Isomerisation	Takasago
Dihydroxylation	Sepracor

The range of reaction types used on the large scale must be expected to expand considerably in the near future. However, progress in heterogeneous asymmetric catalysis, which would have obvious processing advantages (catalyst recovery and use in flow reactors) lags behind and, as yet, fails to match the efficiencies of homogeneous catalysis.

Examples of application to agrochemical targets in Fig. 24 are use of the Sharpless epoxidation in the commercial synthesis of disparlure, the sex attractant of the Gipsy Moth (*Lymantria dispar* (L.)),[57] and application by Takasago of asymmetric isomerisation of pro-chiral

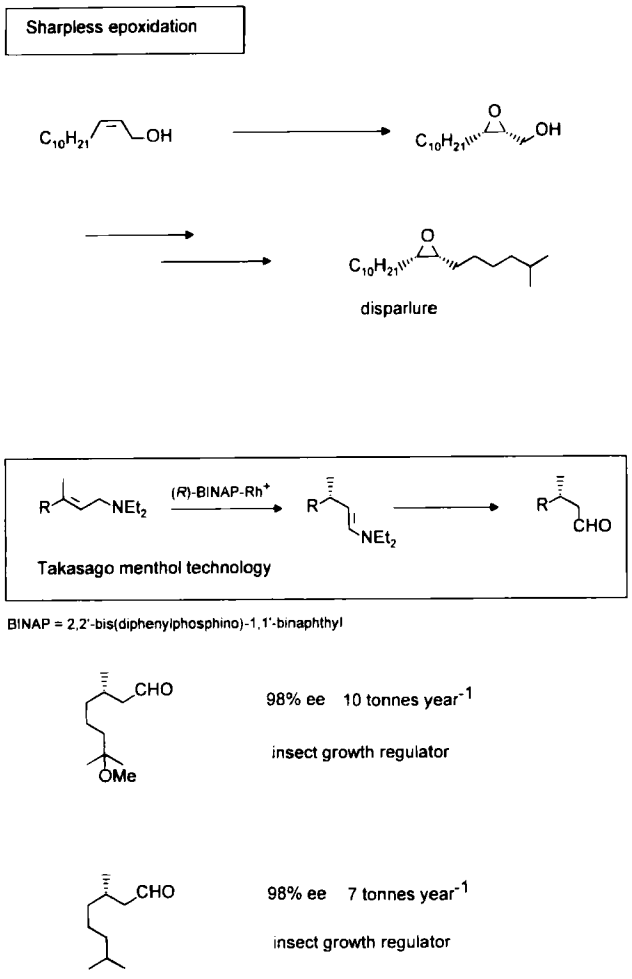


Fig. 24. Applications of chemically-catalysed asymmetric synthesis to the production of agrochemicals.

allylic amines to optically active enamines for tonne-scale production of two insect growth regulators.[58]

Asymmetric cyclopropanation, despite much research activity and its obvious application to pyrethroids, appears only to have been scaled up in the case of the synthesis of a cilastatin intermediate[59] [Fig. 25(a)]. Lack of success with pyrethroids stems from the double challenge of meeting both *cis/trans* selectivity and high ee; this is an order of stereochemical complexity greater than that required for the cilastatin intermediate, where only one chiral centre has to be created. Handling diazo compounds on the production scale must be another disincentive. Figure 25(b) gives an example of what has been achieved in the synthesis of permethrinic acid.[60]

The *potential* for further use of catalytic asymmetric syntheses in agrochemicals production is widespread, as the hydrogenation examples in Fig. 26 illustrate.[61,62]

To realise applications of chemically catalysed asymmetric synthesis requires, ideally, easily synthesised catalysts which are robust and not prone to poisoning, high turnover numbers and/or easy catalyst recycle and avoidance of extreme operating conditions (e.g. very high pressures incur high capital costs).

2.8 The choice between chemistry and biology for asymmetric synthesis

Enantioselective chemical catalysis can often provide a viable alternative to biocatalysis and reactions are possible which have *no natural counterpart*. Biology, on the other hand, can often effect transformations for which there is *no simple chemical equivalent*, effecting in one step transformations which take several chemical steps. A good example of the latter is the biological production of *cis*-diols (Fig. 27).[63,64]

The initial discovery of an enantioselective chemical catalyst has, historically, been far more labour-intensive than screening for a biocatalyst, because of the amount of synthesis required. Biocatalyst screening may be a more empirical process, but it is rapid and statistically favoured because of the large population of organisms from which to choose and the further ability to produce mutants. However, having been discovered, development and scale-up of the bio-catalysed reaction can be more difficult.

As more and different types of enzymes become commercially available it is worth noting that their use has tended to be less restricted, in contrast to key developments in chemical asymmetric synthesis which are generally under much tighter patent control and have to be licensed.

2.9 Physical methods/enabling technologies

Mention must be made of the importance of membrane technologies in the production of chiral molecules, particularly in conjunction with biological methods. Most enzymic reactions are two-phase, and many substrates have low water solubilities; also, biocatalytic processes suffer from inhibition or fail to go to completion. For these and other reasons membranes can be valuable process aids serving to effect separations, to protect the biocatalyst from a harmful environment or as a support for the catalyst.

Professor C. Wandrey, in conjunction with Degussa AG, has developed membrane reactors, principally for amino acid production, in which continuous operation is achieved through use of an ultrafiltration membrane to retain the soluble enzyme. The co-factor is retained by binding it to a water-soluble polymer to increase its molecular weight (Fig. 28(a)).[65] This technology already has a capability to produce amino acids on a scale of several hundred tonnes per year.

Bend Research have developed a system for the indirect chemical regeneration of co-factors. A selectively permeable membrane isolates the production medium from the harsh environment of the regeneration medium (Fig. 28(b)).[66]

Yet another configuration has been developed by Sepracor using a hollow fibre membrane. Here the

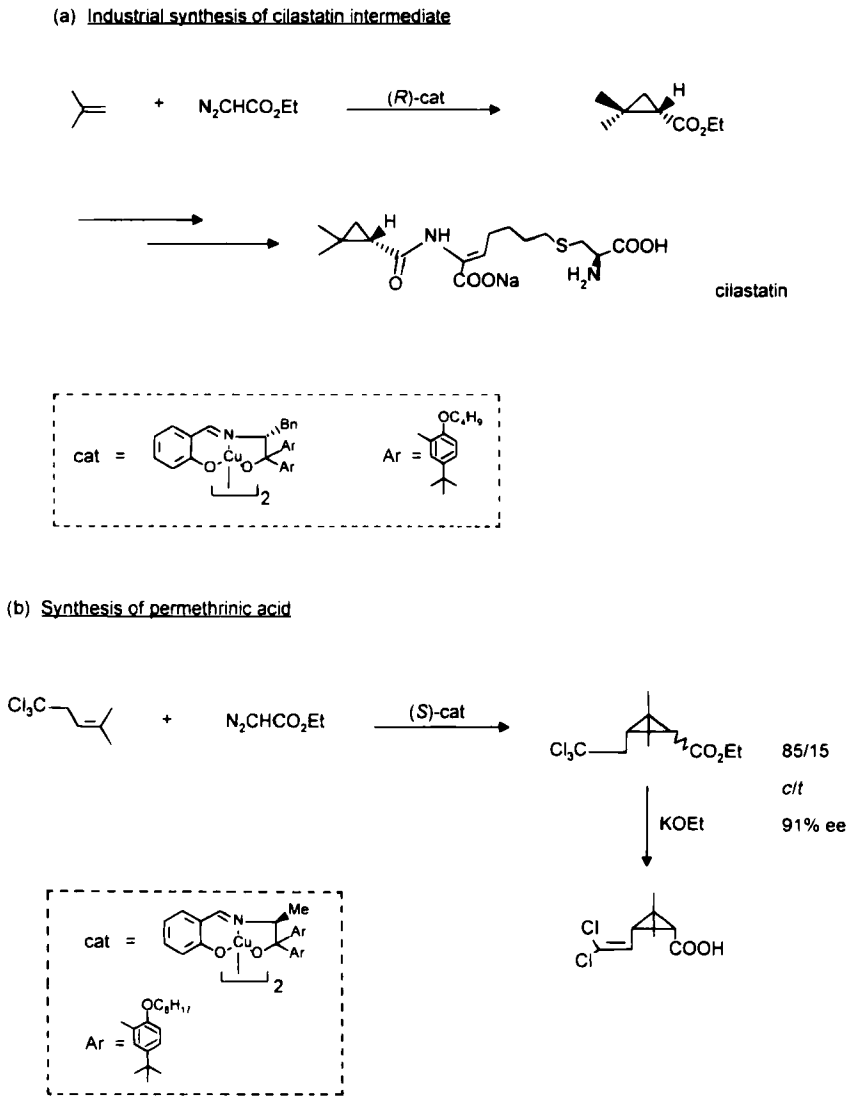


Fig. 25. Asymmetric cyclopropanation.

membrane serves both to support and protect the activity of the enzyme and to facilitate product separation. This has been used in a process for resolution of a pharmaceutical intermediate (Fig. 28(c)) resulting in substantial savings over the classical resolution route.

Another interesting approach is a 'symmetrical' countercurrent extraction/separation of racemates being developed by Akzo; the method does not require functional handles on the substrate and the technology is scale-independent.[67,68] A supported liquid membrane separates countercurrent flows of organic phases containing respectively '*R*' and '*S*' chiral selector molecules. Racemate is introduced into one of the organic streams and partitions between them. Artificial kidney membrane modules have been used, with one chiral liquid flowing through the fibre lumen and the other on the shell side.

Simulated Moving Bed Technology[69] is a countercurrent adsorption process used, for example with zeolite stationary phases, to produce large tonnages of commodity chemicals. It is continuous countercurrent chromatography with continuous feed injection and continuous collection of two product streams. Using chiral LC stationary phases, it is now being developed for separation of chiral substances. Unlike elution chromatography, a portion of the mobile phase is recycled, reducing the overall amount needed. Economics are scale-dependent (in contrast to the above methods where scale-up costs are more nearly linear): separation costs have been estimated at \$200 kg^{-1} on a scale of 40 tonnes $year^{-1}$; issues with this technology which require addressing are the cost and life of the stationary phase as well as solvent recovery costs which are still high because of the dilute feed required.

3 DISCUSSION

This survey has of necessity been brief but shows a large range of options. At the research level, all necessary methods exist for making initial quantities of enantiomers for exploration of property differentiation. There is

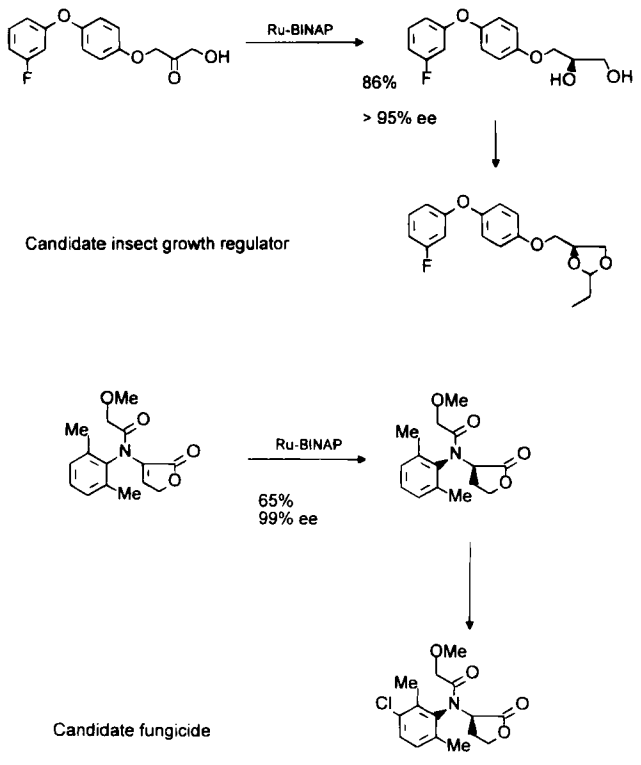


Fig. 26. Catalytic asymmetric hydrogenation.

no longer any question as to whether a desirable isomer can be made but only whether it can be made economically.

The development task is often not an easy one. Although progress in asymmetric synthesis has been rapid over the past decade, over the same period synthesis requirements have also become more demanding. The development of large-scale chiral processes presents an additional challenge to the chemist who is already working in highly constrained circumstances and whose goals are a process that must, *inter alia*, be: safe, non-polluting, selective, high-yielding, have a high space-time yield, use simple plant, provide high quality, operate consistently, use readily available materials, have a fast development time to the final process, be free from patent constraints and deliver on time to meet trials' dates. Superimposed on all of these requirements is the need to produce a single enantiomer with high ee!

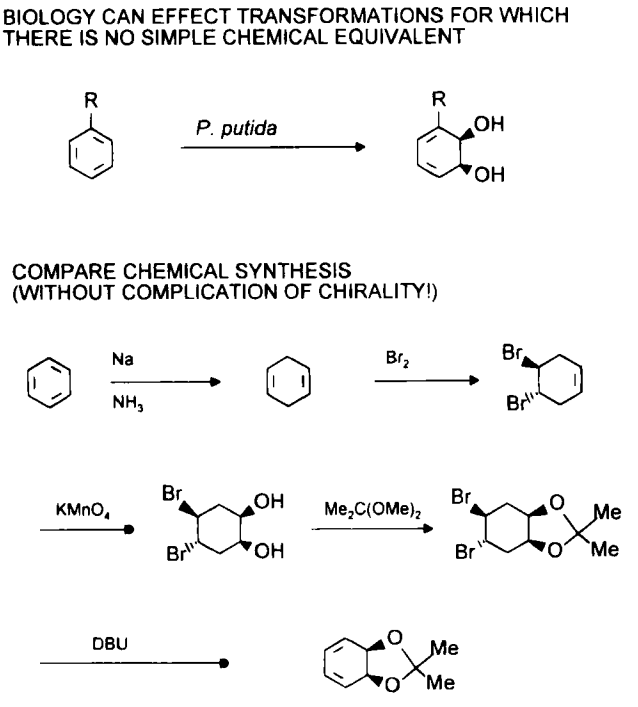


Fig. 27. Chemical and biological approaches to asymmetric synthesis.

No one approach suffices for all situations. It is often useful to begin by considering the best route to the racemate and then to superimpose the stereochemical requirements. However, in the early stage of route development there are usually many ways in which this may be done and any attempt to produce guidelines as to where and how the optical activity should be generated is fraught with exceptions; the best point is rarely predictable. It is often only after physical properties have been determined that this can be settled, as solubility and crystallisation behaviour can be crucial. For example, does a conglomerate exist or is easy enantiomer purification possible? Different route options to a target may be defined solely by the different ways in which the optical activity is created and comparison of these becomes part of the much wider issue of total process economics. All requirements have to be optimised and the 'chiral' part of the equation may become subordinate to other process considerations.

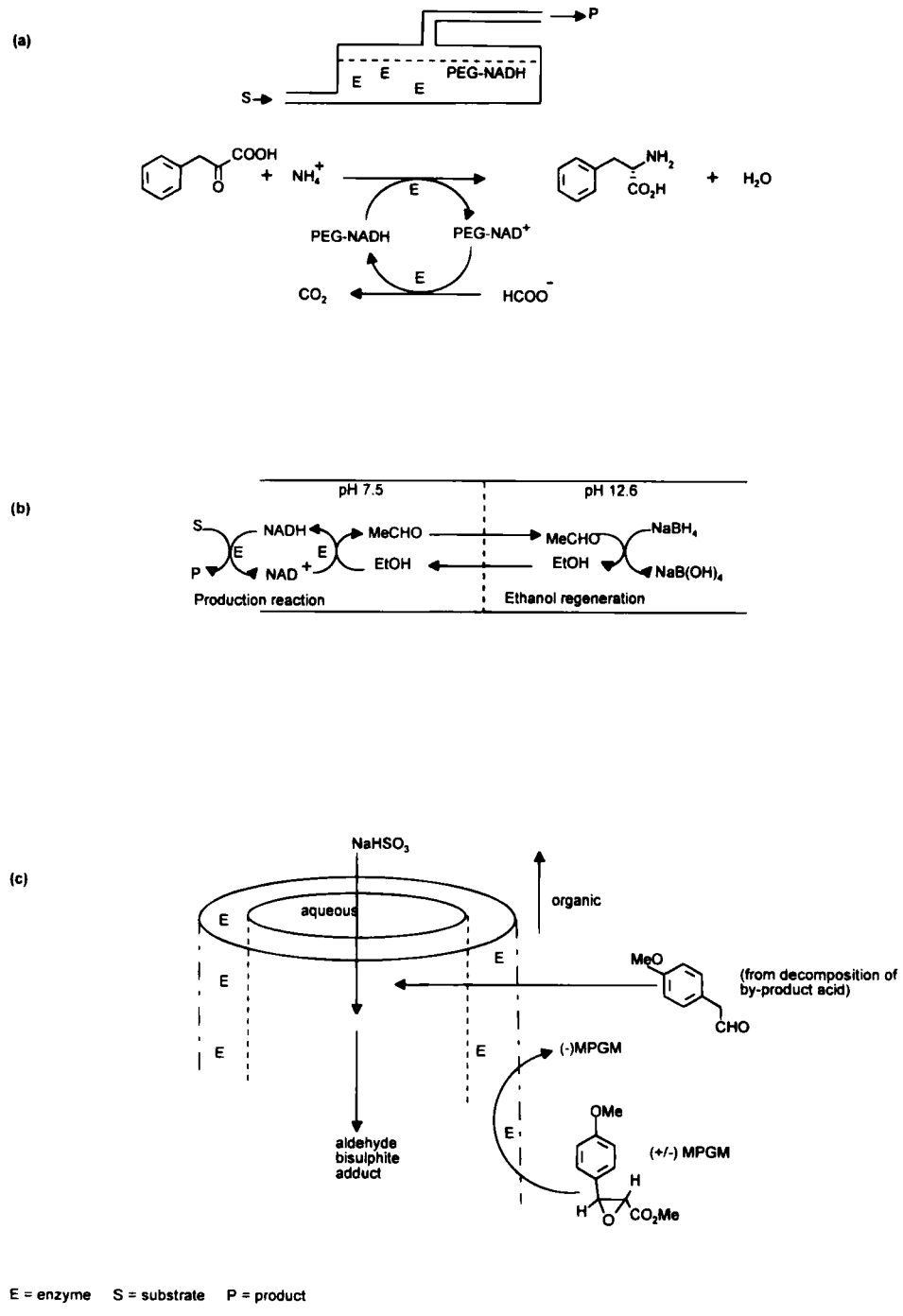


Fig. 28. Examples of uses of membrane technologies.

Much of the future for agrochemicals manufacture is already visible in the guise of pharmaceuticals manufacturing methodology. Price pressures arising from healthcare reforms and generics manufacture should further accelerate development of economic procedures for agrochemicals from within the pharmaceuticals sector.

Single isomer development had hitherto been constrained by the availabilities of techniques, intermediates, catalysts, etc. Now the chiral infrastructure is largely in place and there is no reason why the large-scale production of even moderately priced single enantiomer products should not be contemplated. Agrochemicals are not yet fully utilising the potential of available technology, much of which is inherently capable of meeting cost targets.

Although strenuous efforts may be made to find 'flat' solutions to agrochemicals market needs, the high selectivities now being sought make it inevitable that biological processes are being interfered with at a very fundamental level, and the requirement to engineer enantioselective interactions is inescapable. However,

with the increasing availability of economic chiral technologies there should be less need to compromise between activity and process expedients.

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REFERENCES

1. Tombo, G. M. R. & Bellus, D., Chirality and crop protection. *Angew. Chem. Int. Edn. Engl.*, **30** (1991) 1193–215.
2. Williams, A. J., *Agrochemical Chirality* (DS 70). PJP Publications, Oct. 1992.
3. Anon., Developments in the chiral intermediates market. *Speciality Chemicals*, Jan./Feb. 1994, 6 pp.
4. Gardner, J. C. & DiCicco, R. L., The growth of chiral chemicals—a higher value added technology. *Speciality Chemicals*, July/Aug. 1994, pp. S9–S12.
5. Heaton, A., Agrochemicals: financial importance of pesticides. In *The Chemical Industry*, 2nd edn, ed. A. Heaton. Blackie Academic and Professional, London, 1994, 218 pp.
6. Silvon, M., *Chem. Mkt. Reporter*, 7 Sept. 1992, SR22.
7. Gupta, N. & Eisberg, N., Fine chemicals focused in multinationals' spotlight. *Performance Chemicals*, Aug./Sept. 1991, pp. 19–21.
8. Kelly, D. R., Synthesis of pheromones. *Speciality Chemicals*, Feb. 1995, pp. 68–73.
9. Jones, G. D. G., Pyrethrum production. In *Pyrethrum*, ed. J. E. Casida. Academic Press, New York, 1973, 17 pp.
10. Geoffrey, E., *Ann. Inst. Colon. (Marseilles)*, **2** (1895) 1.
11. Peacock, F. C. In *Jealott's Hill - Fifty Years of Agricultural Research 1928–1978*, ed. F. C. Peacock. The Kynoch Press, Birmingham, UK, 1978, 2 pp.
12. Heaton, A., Agrochemicals: naturally occurring insecticides. In *The Chemical Industry*, 2nd edn, ed. A. Heaton. Blackie Academic and Professional, London, 1994, 253 pp.
13. Mayor, A., Physiologische Eigenschaften der beiden activen Nicotine. *Chem. Ber.*, **37** (1904) 1233–5.
14. Schmeltz, I., Nicotine and other tobacco alkaloids. In *Naturally Occurring Insecticides*, ed. M. Jacobson & D. G. Crosby. Marcel Dekker Inc., New York, 1971, 101 pp.
15. Schmeltz, I., Nicotine and other tobacco alkaloids. In *Naturally Occurring Insecticides*, ed. M. Jacobson & D. G. Crosby. Marcel Dekker Inc., New York, 1971, 102 pp.
16. Sheldon, R. A., Fermentation processes: history of industrial fermentation. In *Chirotechnology*. Marcel Dekker Inc., New York, 1993, 105 pp.
17. For economic aspects of fermentation technology see Sengha, S. S., In *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th edn. Wiley-Interscience, New York, 1993, Vol. 10, 376 pp.
18. See, for example, Crosby, J., Synthesis of optically active compounds: a large-scale perspective. *Tetrahedron*, **47** (1991) 4789–846.
19. Magnus, P. & Roy, G., A short synthesis of (*R*)-(+)-Frontalin and *Latia* Luciferin using new organosilicon reagents. *J. Chem. Soc., Chem. Commun.*, (1978) 297–8.
20. Sobti, R. & Dev, S., (+)-*Trans*-chrysanthemic acid from (+)-δ^3-carene. *Tetrahedron*, **30** (1974) 2927–9.
21. Dev, S., Car-3-ene. A valuable resource for synthesis of some commercially useful chiral molecules. *Proc. Indian Natl. Sci. Acad.*, **54A** (1988) 745–68.
22. Giordano, C., Castaldi, G., Cavicchioli, S. & Villa M., A stereoconvergent strategy for the synthesis of enantiomerically pure (*R*)-(−) and (*S*)-(+)-2-(6-methoxy-2-naphthyl)-propanoic acid (naproxen). *Tetrahedron*, **45** (1989) 4243–52.
23. Lee, S. A., presented at *The 12th SCI Process Development Symposium*, Cambridge, UK, 12–14 Dec. 1994.
24. Enders, D., Alkylation of chiral hydrazones. In *Asymmetric Synthesis*, ed. J. D. Morrison. Academic Press, New York, 1984, Vol. 3, 275 pp.
25. Stinson, S. C., Chiral drugs. *Chem. Eng. News*, 28 Sept. 1992, pp. 46–79.
26. Eliel, E. L., Wilen, S. H. & Mander, L. N., Large scale resolution. In *Stereochemistry of Organic Compounds*. John Wiley and Sons, New York, 1994, 388 pp.
27. Weigel, L. O., presented at *The 12th SCI Process Development Symposium*, Cambridge, UK, 12–14 Dec. 1994.
28. Reider, P. J., Davis, P., Hughes, D. L. & Grabowski, E. J. J., Crystallization-induced asymmetric transformation: stereospecific synthesis of a potent peripheral CCK antagonist. *J. Org. Chem.*, **52** (1987) 955–7.
29. French Patent 2470117, 1980, to Shell; European Patent 106469, 1983, to ICI.
30. Belgian patent 853867, 1977, to Roussel-Uclaf.
31. Jacques, J., Collet, A. & Wilen, S. H., Resolution by direct crystallization. In *Enantiomers, Racemates and Resolutions*. Wiley Interscience, New York, 1981, 217 pp.
32. Collet, A., Strategy and practice of optical resolution mediated by crystallisation techniques. *First Internat. Symp. Separation of Chiral Molecules*, Paris, 31 May–1 June 1988.
33. Anon., First commercial, continuous process to use selective crystallization separates optically active isomers. *Chem. Eng.*, 8 Nov. 1965, 247 pp.
34. Wakamatsu, H., Process that produces monosodium glutamate by synthesis. *Food Eng.*, **40** (1968) 92–5.
35. Jacques, J., LeClercq, M. & Brienne, M-J., La formation de sels augmente-t-elle la fréquence des dédoublements spontanés? *Tetrahedron*, **37** (1981) 1727–33.
36. Black, S. N., Williams, L. J., Davey, R. J., Moffatt, F., Jones, R. V. H., McEwan, D. M. & Sadler, D. E., The preparation of enantiomers of paclobutrazol: a crystal chemistry approach. *Tetrahedron*, **45** (1989) 2677–82.
37. *Enzymes in Organic Synthesis*. Ciba Foundation Symposium 111, Pitman, London, 1985.
38. *Biocatalysts in Organic Synthesis*, ed. J. Tramper, H. C. van der Plas & P. Linko. Elsevier, Amsterdam, 1985.
39. See, for example, Turner, M., Biological catalysis and biotechnology. In *The Chemical Industry*, 2nd edn., ed. A. Heaton. Blackie Academic and Professional, London, 1994, 306 pp.
40. Zaks, A. & Klibanov, A. M., Enzyme-catalyzed processes in organic solvents. *Proc. Natl. Acad. Sci. USA*, **82** (1985) 3192–6.
41. See, for example, de Zoete, M. C., van Dalen, A. C. K., van Rantwijk, F. & Sheldon, R. A., Ester ammoniolysis: a new enzymatic reaction. *J. Chem. Soc., Chem. Commun.*, 1993, 1831–2; (use of lipases to effect aminolysis, a mild procedure for enantioselective synthesis of amides).
42. European Patent 472392, 1991.

43. Hof, R. P. & Kellogg, R. M., Lipase catalysed resolutions of some α,α-disubstitued 1,2-diols in organic solvents; near absolute regio and chiral recognition. *Tetrahedron: Asymmetry*, **5** (1994) 565–8.
44. Hirohara, H., Mitsuda, S., Ando, E. & Komaki, R. In *Biocatalysts in Organic Synthesis*, ed. J. Tramper, H. C. van der Plas & P. Linko. Elsevier, Amsterdam, 1985, 127 pp.
45. Inagaki, M., Hiratake, J., Nishioka, T. & Oda, J'ichi, Lipase-catalyzed kinetic resolution with in-situ racemization: one-pot synthesis of optically active cyanohydrin acetates from aldehydes. *J. Am. Chem. Soc.*, **113** (1991) 9360–1.
46. Dahod, S. K. & Mangano, P.S., Carbon tetrachloride-promoted stereoselective hydrolysis of methyl 2-chloropropionate by lipase. *Biotechnol. Bioeng.*, **30** (1987) 955–9.
47. Bodnár, J., Gubicza, L. & Szabó, L.-P., Enantiomeric separation of 2-chloropropionic acid by enzymatic esterification in organic solvents. *J. Mol. Catal.*, **61** (1990) 353–61.
48. Kirchner, G., Scollar, M. P. & Klibanov, A. M., Resolution of racemic mixtures *via* lipase catalysis in organic solvents. *J. Am. Chem. Soc.*, **107** (1985) 7072–6.
49. Fukui, T., Kawamoto, T., Sonomoto, K. & Tanaka, A., Long-term continuous production of optically active 2-(4-chlorophenoxy)propanoic acid by yeast lipase in an organic solvent system. *Appl. Microbiol. Biotechnol.*, **34** (1990) 330–4.
50. Mutsaers, J. H. G. M. & Kooreman, H. J., Preparation of optically pure 2-aryl- and 2-aryloxy-propionates by selective enzymatic hydrolysis. *Rec. Trav. Chim. Pays-Bas*, **110** (1991) 185–8.
51. Ebiike, H. & Achiwa, K., Lipase-catalysed asymmetric hydrolysis and regioselective bromination of 1,4-dihydropyridine. Synthesis of (*R*)-(+)-Nilvadipine. *Tetrahedron: Asymmetry*, **5** (1994) 1447–50.
52. Crosby, J., Moilliet, J., Parratt, J. S. & Turner, N. J., Regioselective hydrolysis of aromatic dinitriles using a whole cell catalyst. *J. Chem. Soc. Perkin Trans. I* (1994) 1679–87, and references therein.
53. Matcham, G., Bowen, A., Lee, S., Pienkos, P. & Zeitlin, A., Biocatalysis: from new drug development to large scale manufacturing. *Proc. Chiral 94 USA Symp.*, Spring Innovations Ltd, Reston, Virginia, USA 5–6 May 1994, 55 pp.
54. Stirling, D., The use of aminotransferases for the production of chiral amino acids and amines. In *Chirality in Industry*, ed. A. N. Collins, G. N. Sheldrake & J. Crosby. John Wiley and Sons, Chichester, 1992, 209 pp.
55. For good general references see Ref. 57 and *Catalytic Asymmetric Synthesis*, ed. I. Ojima. VCH Publishers, Inc., New York, 1993.
56. Anon., Chemical prices. *Chem. Mkt. Reporter*, 14 Nov. 1994, pp. 38–45.
57. Noyori, R., *Asymmetric Catalysis in Organic Synthesis*. John Wiley and Sons, New York, 1994, 141 pp, and references therein.
58. Noyori, R., Enantiomeric isomerization of olefins. In *Asymmetric Catalysis in Organic Synthesis*. John Wiley and Sons, New York, 1994, 102 pp.
59. Aratani, T., Catalytic asymmetric synthesis of cyclopropanecarboxylic acids: an application of chiral copper carbenoid reaction. *Pure and Appl. Chem.*, **57** (1985) 1839–44.
60. Japan. Kokai Tokkyo Koho 146442, 1976, Kuraray Co., Ltd.
61. Buser, H. P. & Spindler, F., Two enantioselective syntheses of the diol precursor of the biologically most active isomer of an insect growth regulator. *Tetrahedron: Asymmetry*, **4** (1993) 2451–60.
62. Buser, H. P., Pugin, B., Spindler, F., & Sutter, M., Two enantioselective syntheses of a precursor of the biologically most active isomer of CGA 80000 (clozylacon). *Tetrahedron*, **47** (1991) 5709–16.
63. Sheldrake, G. N., Biologically derived arene *cis*-dihydrodiols as synthetic building blocks. In *Chirality in Industry*, ed. A. N. Collins, G. N. Sheldrake & J. Crosby. John Wiley and Sons, Chichester, 1992, 127 pp.
64. Yang, N-c. C., Chen, M-J., Chen, P. & Mak, K. T., Chemistry of heterodimers of benzene and anthracene. *J. Amer. Chem. Soc.*, **104** (1982) 853–5.
65. Bommarius, A. S., Drauz, K., Groeger, U. & Wandrey, C., Membrane bioreactors for the production of enantiomerically pure α-amino acids. In *Chirality in Industry*, ed. A. N. Collins, G. N. Sheldrake & J. Crosby. John Wiley and Sons, Chichester, 1992, 371 pp.
66. van Eikeren, P., Brose, D. J., Muchmore, D. C., West, J. B. & Colton, R. H., Membrane-assisted synthesis methods for the large-scale production of enantiomerically pure pharmaceutical intermediates. *Abstr. Chiral 92 Symp.*, Spring Innovations Ltd, Manchester, UK, 24–25 March 1992, 63 pp.
67. Keurentjes, J. T. F., Nabuurs, L. J. W. M. & Vegter, E. A., A broadly applicable membrane technology for the separation of racemic mixtures. *Abstr. Chiral 94 USA Symp.*, Spring Innovations Ltd, Reston, Virginia, USA, 5–6 May 1994, 39 pp.
68. Netherlands Patent 9201729, 1992, to Akzo.
69. Gattuso, M. J., McCulloch, B. & Priegnitz, J. W., UOP Sorbex simulated moving bed technology. A cost effective route to chiral products. *Abstr. Chiral Europe 94 Symp.*, Spring Innovations Ltd, Nice, France, 19–20 Sept. 1994, 7 pp.